

# Document made available under the Patent Cooperation Treaty (PCT)

International application number: PCT/EP05/050800

International filing date: 25 February 2005 (25.02.2005)

Document type: Certified copy of priority document

Document details: Country/Office: EP

Number: 04004472.9

Filing date: 27 February 2004 (27.02.2004)

Date of receipt at the International Bureau: 19 April 2005 (19.04.2005)

Remark: Priority document submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b)



World Intellectual Property Organization (WIPO) - Geneva, Switzerland  
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Patentanmeldung Nr. Patent application No. Demande de brevet n°

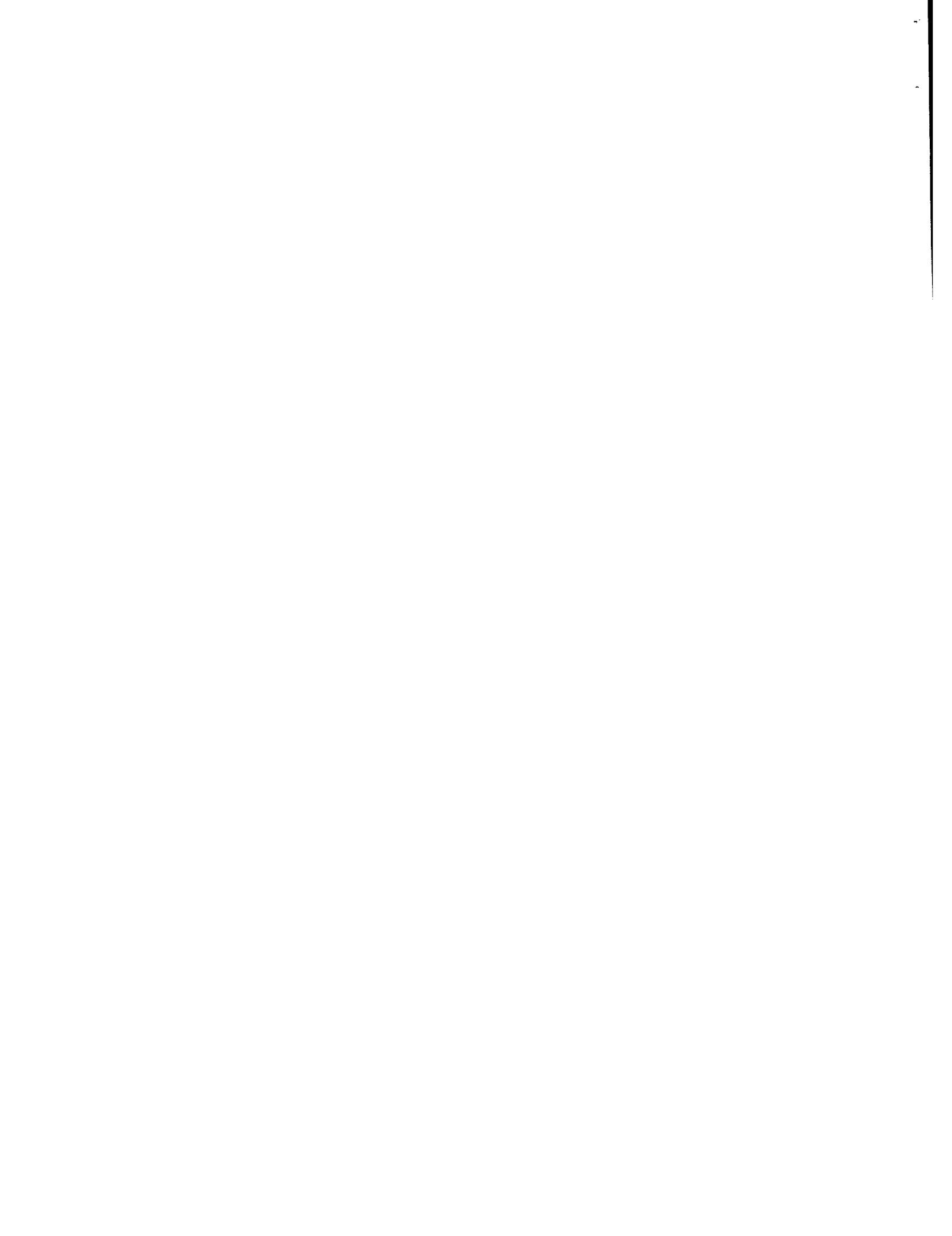
04004472.9

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Im Auftrag

For the President of the European Patent Office

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p.o.

R C van Dijk





Anmeldung Nr:  
Application no.: 04004472.9  
Demande no:

Anmeldetag:  
Date of filing: 27.02.04  
Date de dépôt:

Anmelder/Applicant(s)/Demandeur(s):

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Bezeichnung der Erfindung/Title of the invention/Titre de l'invention:  
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Roflumilast and glycopyrronium combination

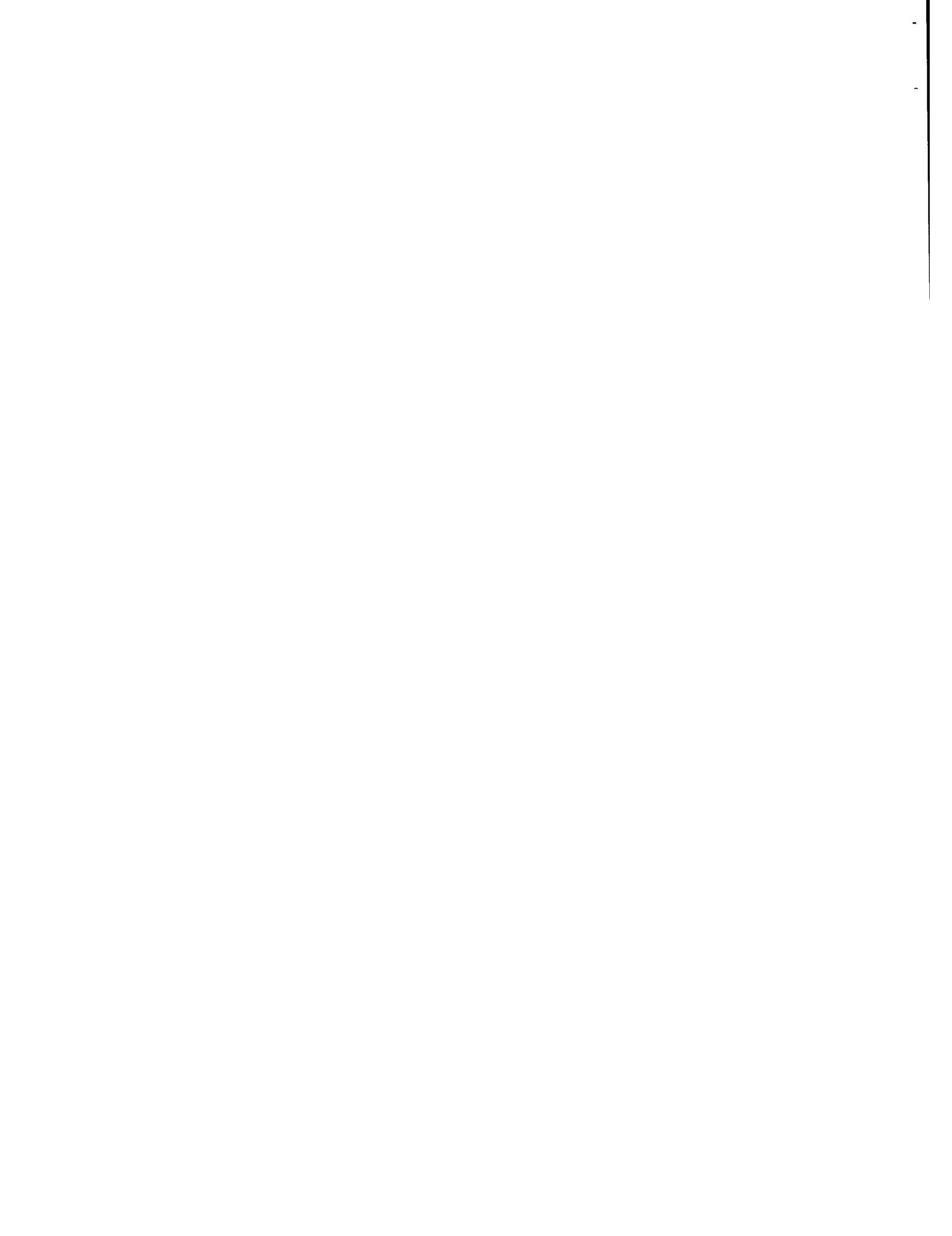
In Anspruch genommene Priorität(en) / Priority(ies) claimed /Priorité(s)  
revendiquée(s)  
Staat/Tag/Aktenzeichen/State/Date/File no./Pays/Date/Numéro de dépôt:

Internationale Patentklassifikation/International Patent Classification/  
Classification internationale des brevets:

A61K31/00

Am Anmeldetag benannte Vertragstaaten/Contracting states designated at date of  
filing/Etats contractants désignées lors du dépôt:

AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LU MC NL  
PT RO SE SI SK TR LI



## Roflumilast and Glycopyrronium Combination

### Field of the Invention

This invention relates to the combination of roflumilast with glycopyrronium, in particular to pharmaceutical formulations containing combinations of roflumilast and glycopyrronium and the use of such pharmaceutical compositions in medicine, in particular in the prophylaxis and treatment of respiratory disease.

### Background

Cyclic nucleotide phosphodiesterase (PDE) inhibitors (specifically of type 4) are currently of special interest as a new generation of active ingredients for treating inflammatory disorders, especially disorders of the airways such as asthma or airway obstructions (such as, for example, COPD = chronic obstructive pulmonary disease). A number of PDE 4 inhibitors are currently undergoing advanced clinical testing, including the compound N-(3,5-dichloropyrid-4-yl)-3-cyclopropylmethoxy-4-difluoromethoxy-benzamide (INN: roflumilast). This and other compounds with a benzamide structure and their use as cyclic nucleotide phosphodiesterase (PDE) inhibitors are described in WO 95/01338.

International patent application WO02/069945 generally describes the combination of a compound from the class of PDE4 inhibitors with a compound from the class of anticholinergic agents for the treatment of respiratory tract disorders. International Patent application WO02/096463 describes an inhaled combination of a selective PDE4 inhibitor and an anticholinergic agent, with the proviso that the anticholinergic agent is not a tiotropium salt. International patent application WO02/096423 describes a combination of therapeutic agents useful in the treatment of obstructive airways and other inflammatory diseases comprising (I) a PDE4 inhibitor that is therapeutically effective in the treatment of said diseases when administered by inhalation; together with (II) an anticholinergic agent comprising a member selected from the group consisting of tiotropium and derivatives thereof that is therapeutically effective in the treatment of said diseases when administered by inhalation. WO 03/011274 is related to treating pulmonary diseases such as obstructive pulmonary disease or asthma by administering a phosphodiesterase 4 inhibitor in combination with an anticholinergic agent. Copyrrolate (Robinul) is mentioned as compound of interest.

WO 01/76575 is related to a pharmaceutical composition for pulmonary delivery which comprises glycopyrrolate in a controlled release formulation, wherein, on administration, the glycopyrrolate exerts its pharmacological effect over a period greater than 12 hours.

WO 00/69468 is related to novel medicament compositions, based on anticholinergic compounds and beta mimetics, which are effective on a long-term basis. The invention also relates to a method for producing the same and to their use in the treatment of diseases of the respiratory tract.

Summary of the invention

It has now been surprisingly found that by combined administration of a pharmaceutical acceptable salt of glycopyrronium and roflumilast a significant unexpected therapeutic benefit, particularly a synergistic therapeutic benefit, in the treatment of inflammatory or obstructive airways diseases can be obtained (such higher FEV1/FVC as compared to monotherapies, dose reduction of the respective mono compounds).

Furthermore, using the compositions of the invention, pharmaceutical compositions, which have a rapid onset and a long duration of action may be prepared. In particular the combination therapy according to the inventions permits the establishment of a twice daily, in particular once daily dosing regimen with consequent substantial benefits in, for example the treatment of obstructive or inflammatory airways diseases (e.g. higher patient compliance, less side effects).

Thus in one aspect the present invention relates to a pharmaceutical formulation comprising a pharmaceutical acceptable salt of glycopyrronium, solvent or physiologically functional derivative thereof in combination with an active pharmaceutical ingredient being a compound selected from the group consisting of roflumilast, pharmaceutically acceptable salts of roflumilast, solvent or physiologically functional derivative thereof and a pharmaceutically acceptable carrier and/or one or more excipients, and optionally one or more other therapeutic ingredients.

Glycopyrrolate { 3-[(Cyclopentyl-hydroxyphenylacetyl)oxy]-1,1-dimethylpyrrolidinium bromide} is an anti-cholinergic drug, has been described for use in the treatment of incontinence (Levin et al, J. Urol., 128:396-398 (1982); Cooke et al., S. Afr. Med. J., 63:3 (1983); R. K. Mirakhur and J. W. Dundee, Anaesthesia, 38:1195-1204 (1983)). Glycopyrrolate has two centers of asymmetry (chiral centers), and can exist in four stereoisometric forms, i.e., two enantiomeric pairs of diastereomers. The two diastereomer pairs have been separated from one another (see, e.g., Demian et al, J. Liq. Chromatog., 13:779-787 (1990)). Commercially available formulations of glycopyrrolate (e.g., Robinul®, a product of A. H. Robins) contain both the (R,S)-glycopyrrolate and (S,R)-glycopyrrolate enantiomers.

US 6204285 discloses methods and compositions for treating urinary incontinence using enantiomerically enriched (R,R)-glycopyrrolate, WO 98/00132 discloses methods and compositions for treating urinary incontinence using enantiomerically enriched (R,S)-glycopyrrolate and WO 98/00133 discloses methods and compositions for treating urinary incontinence using enantiomerically enriched (S,S)-glycopyrrolate. WO 98/021183 discloses enantiomerically pure pharmaceutically suitable salt of glycopyrronium [S,S-, S,R, R,S- and R,R-forms] and the use in the treatment of spasms of the smooth musculature of the gastrointestinal tract and for treating obstructive respiratory disorders.

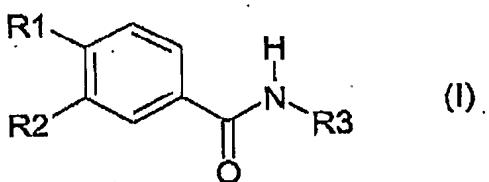
Pharmaceutical acceptable salt of glycopyrronium in connection with the invention refers to pharmaceutically acceptable salts normally used in pharmaceutical technology. Pharmacologically acceptable salts, which may be mentioned in connection with glycopyrronium are the bromide, chloride, phosphate,

nitrate, sulfate, citrate, fumarate, propionate, tartrate, iodide, benzoate, methansulfonate or tosylate. In a preferred embodiment of the invention the salt is the bromide salt.

Pharmaceutical acceptable salt of glycopyrronium in connection with the invention refers to the racemic forms [S,S-, S,R, R,S- and R,R-forms] of the pharmaceutical acceptable salt of glycopyrronium in any mixing ratio and preferably to the enantiomerically enriched S,S-, S,R, R,S- and R,R-forms of the pharmaceutical acceptable salt of glycopyrronium (i.e. pharmaceutically acceptable salt of (3S,2'S)-3-[(cyclopentylhydroxyphenylacetyl)oxy]-1,1-dimethylpyrrolidinium, pharmaceutically acceptable salt of (3S,2'R)-3-[(cyclopentylhydroxyphenylacetyl)oxy]-1,1-dimethylpyrrolidinium, pharmaceutically acceptable salt of (3R,2'S)-3-[(cyclopentylhydroxyphenylacetyl)oxy]-1,1-dimethylpyrrolidinium and pharmaceutically acceptable salt of (3R,2'R)-3-[(cyclopentylhydroxyphenylacetyl)oxy]-1,1-dimethylpyrrolidinium). In a preferred embodiment of the invention the enantiomerically enriched form of the pharmaceutical acceptable salt of glycopyrronium is the R,R-form (i.e. (3R,2'R)-3-[(cyclopentylhydroxyphenylacetyl)oxy]-1,1-dimethylpyrrolidinium). Enantiomerically enriched in connection with the invention refers to a pharmaceutical acceptable salt of glycopyrronium with an enantiomeric purity of 90% minimum enantiomeric excess (ee), preferably 95 % ee, more preferably more than 98 % ee, and in particular preferably more than 99.5 % ee. In a preferred embodiment of the invention the pharmaceutical acceptable salt of glycopyrronium in connection refers to an pharmaceutical acceptable salt of (3R,2'R)-3-[(cyclopentylhydroxyphenylacetyl)oxy]-1,1-dimethylpyrrolidinium) which substantially does not contain glycopyrronium in the S,S-, S,R- and/or R,S- forms. In a further preferred embodiment of invention the pharmaceutical acceptable salt of glycopyrronium refers to (3R,2'R)-3-[(cyclopentylhydroxyphenylacetyl)oxy]-1,1-dimethylpyrrolidinium) bromide, preferably enantiomerically enriched with an minimum ee of 99.5 %.

The pharmaceutically acceptable salts of glycopyrronium may be prepared as disclosed in US 6204285 WO 98/00132, WO 98/00133, and WO 98/021183.

Roflumilast (hereinafter also referred to as active ingredient) is the INN for a compound of the formula I



in which

- R1 is difluoromethoxy,
- R2 is cyclopropylmethoxy and
- R3 is 3,5-dichloropyrid-4-yl.

This compound has the chemical name N-(3,5-dichloropyrid-4-yl)-3-cyclopropylmethoxy-4-difluoromethoxybenzamide (INN: roflumilast). By the term "physiologically functional derivative" is meant a

chemical derivative of roflumilast having the same physiological function as roflumilast, for example, by being convertible in the body thereto or by being an active metabolite of roflumilast. Physiological functional derivatives of roflumilast, which may be mentioned in connection with the invention are for example the N-oxide of roflumilast, and its salts and solvents. The N-oxide of roflumilast has the chemical name 3-cyclopropylmethoxy-4-difluoromethoxy-N-(3,5-dichloropyrid-4-yl 1-oxide)benzamide. This compound of the formula I, its salts, the N-oxide, its salts and the use of these compounds as phosphodiesterase (PDE) 4 inhibitors are described in the international patent application WO 95/01338.

Salts suitable for compounds of the formula I - depending on the substitution - are all acid addition salts but, in particular, all salts with bases. Particular mention may be made of the pharmacologically acceptable salts of the inorganic and organic acids and bases normally used in pharmaceutical technology. Pharmacologically unacceptable salts, which, for example, may be the initial products of the process for preparing the compounds of the invention on the industrial scale are converted into pharmacologically acceptable salts by processes known to the skilled worker. Those suitable on the one hand are water-soluble and water-insoluble acid addition salts with acids such as, for example, hydrochloric acid, hydrobromic acid, phosphoric acid, nitric acid, sulfuric acid, acetic acid, citric acid, D-gluconic acid, benzoic acid, 2-(4-hydroxybenzoyl)benzoic acid, butyric acid, sulphosalicylic acid, maleic acid, lauric acid, malic acid, fumaric acid, succinic acid, oxalic acid, tartaric acid, embonic acid, stearic acid, toluenesulphonic acid, methanesulphonic acid, or 3-hydroxy-2-naphthoic acid, the acids being employed to prepare the salts in the equimolar ratio of amounts, or one differing therefrom - depending on whether the acid is monobasic or polybasic and depending on which salt is desired.

On the other hand, salts with bases are also particularly suitable. Examples of basic salts which may be mentioned are lithium, sodium, potassium, calcium, aluminium, magnesium, titanium, ammonium, meglumine or guanidinium salts, once again the bases being employed to prepare the salts in the equimolar ratio of amounts or one differing therefrom.

It will be appreciated that the compounds of the combination may be administered simultaneously, either in the same pharmaceutical formulation (hereinafter also referred to as fixed combination) or in different pharmaceutical formulations (hereinafter also referred to as free combination) or sequentially in any order. If there is sequential administration, the delay in administering the second compound should not be such as to lose the beneficial therapeutic effect of the combination. As an example, both drugs may be provided separately as oral formulations, or one may be an oral preparation and the other an inhalant, or both may be provided in a form suitable for inhalation. Administration may be at the same time. Or they may be administered either close in time or remotely, such as where one drug is administered in the morning and the second drug is administered in the evening.

As mentioned above, both the pharmaceutical acceptable salt of glycopyrronium and roflumilast and their pharmaceutically acceptable salts, solvates, and physiologically functional derivatives have been

described for use in the treatment of respiratory diseases. Therefore, formulations of pharmaceutical acceptable salt of glycopyrronium and roflumilast pharmaceutically acceptable salts, solvates, and physiologically functional derivatives have use in the prophylaxis and treatment of clinical conditions for which a PDE 4 inhibitor and/or an anticholinergic compound is indicated. Such conditions include diseases associated with reversible airways obstruction such as asthma, nocturnal asthma, exercise-induced asthma, chronic obstructive pulmonary diseases (COPD) (e. g. chronic and wheezy bronchitis, emphysema), respiratory tract infection and upper respiratory tract disease (e. g. rhinitis, such as allergic and seasonal rhinitis). The combination may be administered prophylactically or after onset of symptoms.

Accordingly, the present invention also provides a method for the prophylaxis or treatment of a clinical condition in a mammal, such as a human, for which a PDE 4 inhibitor and/or an anticholinergic compound is/are indicated, which comprises administration of a therapeutically effective amount of a pharmaceutical formulation comprising roflumilast or a pharmaceutical acceptable salt, solvate, or physiologically functional derivative thereof and a pharmaceutical acceptable salt of glycopyrronium, a solvate, or physiologically functional derivative thereof, and a pharmaceutical acceptable carrier and/or one or more excipients. In a preferred aspect, there is provided such a method, which comprises administration of a therapeutically effective amount of a combination comprising roflumilast and pharmaceutical acceptable salt of glycopyrronium, and a pharmaceutical acceptable carrier and/or one or more excipients. In particular, the present invention provides such a method for the prophylaxis or treatment of a disease associated with reversible airways obstruction such as asthma, chronic obstructive pulmonary disease (COPD), respiratory tract infection or upper respiratory tract disease.

The amount of roflumilast or a pharmaceutical acceptable salt, solvate or physiologically functional derivative thereof and pharmaceutical acceptable salt of glycopyrronium which is required to achieve a therapeutic effect will, of course, vary with the particular compound, the route of administration, the subject under treatment, and the particular disorder or disease being treated.

The dosage of roflumilast is of the order of magnitude customary for PDE4 inhibitors, it being possible to administer the daily dose in one or more dosage units. The normal dose on systemic therapy (oral) is between 0.001mg and 3mg per kilogram and day. Oral dosage forms according to the invention contain from 0.01mg to 5mg of roflumilast, preferably from 0.05mg to 2.5mg, particularly preferably 0.1mg to 0.5mg of roflumilast per dosage unit. Examples of oral dosage forms (tablets) contain 0.1mg, 0.125mg, 0.25mg and 0.5mg of roflumilast per dosage unit. Normally, one or more than one dosage unit of the invention is administered once a day. If desired, it is also possible for one or more dosage units of the invention to be administered more than once a day. Dosage forms for inhalation according to the invention contain from 0.01mg to 5mg of roflumilast, preferably from 0.05mg to 2.5mg, particularly preferably 0.1mg to 0.5mg of roflumilast per dosage unit. Examples of inhalative dosage units (e.g. Inhalation capsules) contain Roflumilast in a dose range of 0.01mg up to 2.0 mg, preferably 0.05mg, 0.1mg, 0.125mg, 0.25mg or 0.5mg of roflumilast per dosage unit.

The dosage of the pharmaceutically acceptable salt of glycopyrronium is in the order of magnitude customary for glycopyrronium for the treatment of respiratory diseases for example in the range from 0.1 to 1000 µg.

It is preferred in connection with the present invention to have a twice daily and particularly preferred to have a once daily dosing regimen.

Suitably, the pharmaceutical formulations for inhalation according to the invention comprise the active ingredients in amounts such that in case of administration by inhalation from inhalers each actuation provides a therapeutically effective dose, for example, a dose of roflumilast in a range of 0.01mg up to 2.0 mg, preferably of 10µg to 500µg, 50µg to 350µg or 100µg to 250µg and a dose of pharmaceutical acceptable salt of glycopyrronium in a range of 0.1 to 1000µg preferably 30µg, 60µg and 120µg. It is particularly preferred that each actuation provide a dose therapeutically effective for a twice daily dosing regimen or more particularly preferred for a once daily dosing regimen.

Suitably, the pharmaceutical formulations for inhalation according to the invention provide therapeutically effective doses that permit the establishment of a twice daily (bis in diem – b. i. d) dosing regimen and in particular a once daily dosing regimen.

The formulations include those suitable for oral, parenteral (including subcutaneous, intradermal, intramuscular, intravenous and intraarticular, intranasal, inhalation (including fine particle dusts or mists which may be generated by means of various types of metered dose pressurised aerosols, nebulisers liquid-based inhalers equipped with appropriate aerolization technologies/apparatus or insufflators), rectal and topical (including dermal, buccal, sublingual and intraocular administration) although the most suitable route may depend upon for example the condition and disorder of the recipient. The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing the active ingredients into association with the carrier, which constitutes one or more accessory ingredients/excipients. In general the formulations are prepared by uniformly and intimately bringing into association the active ingredients with liquid carriers or finely divided solid carriers or both and then, if necessary, shaping the product into the desired formulation.

In one embodiment of the invention roflumilast is provided as oral administration form and pharmaceutical acceptable salt of glycopyrronium is provided in a form suitable for inhalation. In this embodiment pharmaceutical acceptable salt of glycopyrronium is preferably provided in the form of a powder composition suitable for dry powder inhalation. Preferably roflumilast is provided in tablet form when given as oral administration form.

In another embodiment of the invention the pharmaceutical acceptable salt of glycopyrronium and roflumilast are provided in form suitable for inhalation. Both active ingredients may be provided in separate dosage forms (free combination) and preferably in a fixed combination.

Formulations for inhalation include powder compositions, which will preferably contain lactose, and spray compositions which may be formulated, for example, as aqueous solutions or suspensions or as aerosols delivered from pressurised packs, with the use of a suitable propellant, e. g. 1, 1, 1, 2-terfluoroethane, 1, 1, 1, 2, 3, 3-heptafluoropropane, carbon dioxide or other suitable gas. A class of propellants, which are believed to have minimal ozone-depleting effects in comparison to conventional chlorofluorocarbons comprise hydrofluorocarbons and a number of medicinal aerosol formulations using such propellant systems are disclosed in, for example, EP 0372777, W091/04011, W091/11173, W091/11495, W091/14422, W093/11743, and EP-0553298. These applications are all concerned with the preparation of pressurised aerosols for the administration of medicaments and seek to overcome problems associated with the use of this new class of propellants. In particular the problems of stability associated with the pharmaceutical formulations prepared. The applications propose, for example, the addition of one or more of excipients such as polar cosolvents or wetting agents (e.g. alcohols such as ethanol), alkanes, dimethyl ether, surfactants (including fluorinated and non-fluorinated surfactants, carboxylic acids such as oleic acid, polyethoxylates etc.) or bulking agents such as a sugar (see for example WO02/30394) and amino acids and vehicles such as cromoglicic acid and/or nedocromil which are contained at concentrations, which are not therapeutically and prophylactically active (see WO00/07567). For suspension aerosols, the active ingredients should be micronised so as to permit inhalation of substantially all of the active ingredients into the lungs upon administration of the aerosol formulation, thus the active ingredients will have a mean particle size of less than 100 microns, desirably less than 20 microns, and preferably in the range 0.7 to 10 microns, for example, 1 to 5 microns.

Canisters generally comprise a container capable of withstanding the vapour pressure of the propellant, such as plastic or plastic-coated glass bottle or a metal can, for example an aluminium can which may optionally be anodised, lacquer-coated and/or plastic-coated, which container is closed with a metering valve. Canisters may be coated with a fluorocarbon polymer as described in WO 96/32150, for example, a co-polymer of polyethersulphone (PES) and polytetrafluoroethylene (PTFE). Another polymer for coating that may be contemplated is FEP (fluorinated ethylene propylene).

The metering valves are designed to deliver a metered amount of the formulation per actuation and incorporate a gasket to prevent leakage of propellant through the valve. The gasket may comprise any suitable elastomeric material such as for example low density polyethylene, chlorobutyl, black and white butadiene-acrylonitrile rubbers, butyl rubber and neoprene. Thermoplastic elastomer valves as described in W092/11190 and valves containing EPDM rubber as described in W095/02650 may be suitable. Suitable valves are commercially available from manufacturers well known in the aerosol industry, for example, from Valois, France (eg. DF10, DF30, DF60), Bespak plc, UK (eg. BK300, BK356, BK357) and 3M-Neotechnic Ltd, UK (eg. Spraymiser).

Valve seals, especially the gasket seal and also the seals around the metering chamber, can be manufactured of a material, which is inert to and resists extraction into the contents of the formulation, especially when the contents include ethanol.

Valve materials, especially the material of manufacture of the metering chamber, can be manufactured of a material which is inert to and resists distortion by contents of the formulation, especially when the contents include ethanol. Particularly suitable materials for use in manufacture of the metering chamber include polyesters eg polybutyleneterephthalate (PBT) and acetals, especially PBT.

Materials of manufacture of the metering chamber and/or the valve stem may desirably be fluorinated, partially fluorinated or impregnated with fluorine containing substances in order to resist drug deposition.

Valves, which are entirely or substantially composed of metal components (eg Spraymiser, 3M-Neotechnic), are especially preferred for use according to the invention.

Intranasal sprays or nasal drops may be formulated with aqueous or non-aqueous vehicles with or without the addition of agents such as thickening agents, buffer salts or acid or alkali to adjust the pH, isotonicity adjusting agents, preservatives or anti-oxidants.

In another embodiment of the invention the pharmaceutical formulation comprising the pharmaceutical acceptable salt of glycopyrronium in combination with roflumilast is a dry powder, i.e. roflumilast and the pharmaceutically acceptable salts of glycopyrronium are present in a dry powder comprising finely divided pharmaceutical acceptable salt of glycopyrronium and roflumilast optionally together with a finely divided pharmaceutically acceptable carrier, which is preferably present and may be one or more materials known as carriers in dry powder inhalation compositions, for example saccharides, including monosaccharides, disaccharides, polysaccharides and sugar alcohols such as arabinose, glucose, fructose, ribose, mannose, sucrose, trehalose, lactose, maltose, starches, dextran or mannitol. An especially preferred carrier is lactose, particularly in the form of the monohydrate. The dry powder may be in capsules of gelatine or plastic, or in blisters, for use in a dry powder inhalation device, preferably in dosage units of the mixture of pharmaceutical acceptable salt of glycopyrronium and roflumilast together with the carrier in amounts to bring the total weight of powder in each capsule to from 5mg to 50mg. Alternatively the dry powder may be contained in a reservoir of a multi-dose dry powder inhalation device. Capsules and cartridges of for example gelatin, or blisters of for example laminated aluminium foil, for use in an inhaler or insulator may be formulated containing a powder mix of the active ingredients and a suitable powder base such as lactose or starch, preferably lactose. In this aspect, the active ingredients are suitably micronised so as to permit inhalation of substantially all of the active ingredients into the lungs upon administration of the dry powder formulation, thus the active ingredients will have a particle size of less than 100 $\mu$ m, desirably less than 20 $\mu$ m, and preferably in the range 1 to 10 $\mu$ m. The solid carrier, where present, generally has a maximum particle diameter of 300 $\mu$ m, preferably 200 $\mu$ m, and conveniently has a mean particle diameter of 40 to 100 $\mu$ m, preferably 50 to 75 $\mu$ m. The

particle size of the active ingredients and that of a solid carrier where present in dry powder compositions, can be reduced to the desired level by conventional methods, for example by grinding in an air-jet mill, ball mill or vibrator mill, microprecipitation, spray drying, lyophilisation or recrystallisation from supercritical media.

Where the inhalable form of the composition of the invention is the finely divided particulate form, the Inhalation device may be, for example a dry powder inhalation device adapted to deliver dry powder from a capsule or blister containing a dosage unit of the dry powder or a multi-dose dry powder inhalation device. Such dry powder inhalation devices are known in the art. Examples which may be mentioned are Cyclohaler®, Diskhaler®, Rotadisk®, Turbohaler®, Novolizer® or the dry powder inhalation devices disclosed EP 0 505 321, EP 407028, EP 650410, EP 691865 or EP 725725 (Ultrahaler®).

Formulations for inhalation by nebulization may be formulated with an aqueous vehicle with the addition of agents such as acid or alkali, buffer salts, isotonicity adjusting agents or antimicrobials. They may be sterilised by filtration or heating in an autoclave. Suitable technologies for this type of administration are known in the art. As an example the Mystic® technology is to be mentioned (see for example US6397838, US8454193 and US6302331) as well as the Respimat® technology or e-flow technology by Pari.

Preferred unit dosage formulations are those containing a pharmaceutical effective dose, as hereinbefore recited, or an appropriate fraction thereof, of the active ingredient. Thus, in the case of formulations designed for delivery by metered dose pressurised aerosols, one actuation of the aerosol may deliver half of the therapeutical effective amount such that two actuations are necessary to deliver the therapeutically effective dose.

It should be understood that in addition to the ingredients particularly mentioned above, the formulations of this invention may include other agents conventional in the art having regard to the type of formulation in question. Furthermore, the claimed formulations include bioequivalents as defined by the US Food and Drugs Agency.

The invention will now be illustrated by the following examples without restricting it.

**Fixed Combinations****Example 1: Powder Inhaler (mono dose system based on inhalation capsule)**

240 mg micronised R,R-glycopyrronium bromide, 400mg micronised roflumilast and 28,8g lactose monohydrate (Ph. Eur. 4) are mixed in a turbula mixer in two steps. The blend is screened (0.71mm sieve) and transferred to the container of a planetary mixer. After adding with additional 70.0g lactose monohydrate and mixing, 25mg of the blend are filled into capsules of size 3, which can be administered with a powder inhaler. One capsule contains 60 $\mu$ g R,R-glycopyrronium bromide and 100 $\mu$ g of roflumilast.

**Example 2: Powder Inhaler (multi dose system)**

1000g lactose monohydrate (Ph. Eur. 4) is screened by a sieve-mill. 2.5g roflumilast micronised (screened; 0.5 mm sieve) and 147,5g of deagglomerated lactose monohydrate are blended in a turbula mixer. 195g of deagglomerated lactose monohydrate are filled in a high shear mixer and 1.5 g R,R-glycopyrronium bromide micronised (screened, 0.5 mm sieve) are added to form a blend. The roflumilast lactose pre-blend is screened (0.5 mm sieve), added to the container of a high shear mixer and mixed with the R,R-glycopyrronium bromide lactose blend. Subsequently 650g of deagglomerated lactose monohydrate are added and mixed. 1.5g of the blend are filled in the reservoir of a multi dose powder inhaler. After fully assembling, the powder inhaler is wrapped into a protective foil to achieve moisture protection. Such powder inhaler will contain 60 single doses (20mg powder) each containing 30 $\mu$ g R,R-glycopyrronium bromide and 50 $\mu$ g roflumilast.

**Example 3: Powder Inhaler (multi dose system)**

5.33g micronised roflumilast and 14.7g lactose monohydrate (Ph. Eur. 4) are screened (0.5 mm sieve) and mixed in a turbula mixer. The blend obtained is screened (0.5 mm sieve) and together with micronised R,R-glycopyrronium bromide (screened; mesh 0.5 mm) and 169.3g lactose monohydrate (Ph. Eur. 4) filled in a steel batching vessel and blended in a turbula mixer. 1.2g of the blend thus obtained is filled in the powder reservoir of a powder inhaler. After fully assembling the powder inhaler is wrapped in a protective foil to achieve protection from moisture. Such powder inhaler may contain at least 120 single doses (7.5 mg powder) each having 120 $\mu$ g R,R-glycopyrronium bromide and 200 $\mu$ g roflumilast.

**B. Free Combinations**

**Example 1:** R,R-glycopyrronium bromide is provided in a form suitable for administration by inhalation. Roflumilast is provided as pharmaceutical product for oral administration.

Roflumilast Tablet

Weight based on a tablet containing 0.1 mg of roflumilast

1. Roflumilast (micronized)	0.100 mg
2. Lactose monohydrate	49.660 mg
3. Corn starch	13.390 mg
4. Polyvidone K90	1.300 mg
5. Magnesium stearate (vegetable)	0.650 mg
<b>Total</b>	<b>65.100 mg</b>

Production: (1) is mixed with part of (3), and a trituration is produced in a planetary mill. The trituration is put together with (2) and the remaining amount of (3) in the product container of a fluidized bed granulation system, and a 5% granulation solution of (4) in purified water is sprayed on and dried under suitable conditions. (5) is added to the granules, and the mixture obtained after mixing is compressed in a tablet press to tablets having an average weight of 65.1 mg.

Weight based on a tablet containing 0.125 mg of roflumilast

1. Roflumilast	0.125 mg
2. Lactose monohydrate	49.660 mg
3. Corn starch	13.390 mg
4. Polyvidone K90	1.300 mg
5. Magnesium stearate (vegetable)	0.650 mg
<b>Total</b>	<b>65.125 mg</b>

Production: (1) is mixed with part of (3), and a trituration is produced in a planetary mill. The trituration is put together with (2) and the remaining amount of (3) in the product container of a fluidized bed granulation system, and a 5% granulation solution of (4) in purified water is sprayed on and dried under suitable conditions. (5) is added to the granules, and the mixture obtained after mixing is compressed in a tablet press to tablets having an average weight of 65.125 mg.

Weight based on a tablet containing 0.25 mg of roflumilast

1. Roflumilast	0.250 mg
2. Microcrystalline cellulose	33.900 mg

3.	Corn starch	2.500 mg
4.	Polyvidone K90	2.250 mg
5.	Sodium carboxymethylstarch (type A)	20.000 mg
6.	Magnesium stearate (vegetable)	0.600 mg
	<b>Total</b>	<b>59.500 mg</b>

Production: (1) is mixed with part of (3), and a trituration is produced in a planetary mill. The trituration is put together with (2), (5) and the remaining amount of (3) in the product container of a fluidized bed granulation system, and a 5% granulation solution of (4) in purified water is sprayed on and dried under suitable conditions. (6) is added to the granules, and the mixture obtained after mixing is compressed in a tablet press to tablets having an average weight of 59.5 mg.

Although the invention has been described in terms of preferred formulations and ingredients, it will be understood that these are not intended to be limiting. To the contrary, those skilled in the art will understand that various optional ingredients may be included, such as flavouring agents, preservatives, additional active ingredients, and the like, while still embodying the present invention.

Claims

1. A pharmaceutical formulation comprising a pharmaceutical acceptable salt of glycopyrronium, a solvates or physiologically functional derivative thereof in combination with an active pharmaceutical ingredient being a compound selected from the group consisting of roflumilast, pharmaceutically acceptable salts of roflumilast, solvates or physiologically functional derivative thereof and a pharmaceutically acceptable carrier and/or one or more excipients, and optionally one or more other therapeutic ingredients.
2. Formulation according to claim 1, wherein pharmaceutical acceptable salt of glycopyrronium and roflumilast are contained in the same pharmaceutical formulation (fixed combination).
3. Formulation according to claim 1, wherein pharmaceutical acceptable salt of glycopyrronium and roflumilast are contained in different pharmaceutical formulations (free combination).
4. Formulation according to claim 1, comprising a compound selected from the group of N-(3,5-dichloropyrid-4-yl)-3-cyclopropylmethoxy-4-difluoromethoxybenzamide, 3-cyclopropylmethoxy-4-difluoromethoxy-N-(3,5-dichloropyrid-4-yl 1-oxide)benzamide and salts or solvates thereof.
5. Formulation according to claim 1, wherein the pharmaceutical acceptable salt of glycopyrronium is selected from the group of compounds racemic forms [S,S-, S,R, R,S- and R,R-forms] of the pharmaceutical acceptable salt of glycopyrronium in any mixing ratio and enantiomerically enriched S,S-, S,R, R,S- and R,R-forms of the pharmaceutical acceptable salt of glycopyrronium.
6. Formulation according to claim 5, wherein the enantiomerically enriched form of the pharmaceutical acceptable salt of glycopyrronium is the R,R-form (i.e. (3R,2'R)-3-[(cyclopentylhydroxyphenylacetyl)oxy]-1,1-dimethylpyrrolidinium).
7. Formulation according to claim 6, wherein the R,R-form has an enantiomeric purity of 90% minimum enantiomeric excess (ee), preferably 95 % ee, more preferably more than 98 % ee, and in particular preferably more than 99.5 % ee.
8. Formulation according to claim 1 wherein the pharmaceutical acceptable salt of glycopyrronium is (3R,2'R)-3-[(cyclopentylhydroxyphenylacetyl)oxy]-1,1-dimethylpyrrolidinium bromide, which substantially does not contain glycopyrronium in the S,S-, S,R- and/or R,S- forms.

9. Formulation according to claim 1, comprising pharmaceutical acceptable salt of glycopyrronium and roflumilast in an amount and ratio to be effective for a twice or once daily treatment of a clinical condition in a mammal, such as a human, for which a PDE 4 inhibitor and/or an anticholinergic agent is indicated.
10. Formulation according to claim 1, which is suitable for administration by inhalation.
11. Formulation according to claim 1, which is suitable for nasal administration.
12. Formulation according to claim 1, wherein roflumilast is present in a form for oral administration and a pharmaceutical acceptable salt of glycopyrronium is present in a form suitable for administration by inhalation.
13. Pharmaceutical formulation according to claim 1, which is a dry powder and the carrier is a saccharide.
14. Pharmaceutical formulation according to claim 13, wherein the carrier is lactose monohydrate.
15. Method for the prophylaxis or treatment of a clinical condition in a mammal, such as a human, for which a PDE 4 inhibitor and/or an anticholinergic agent is indicated, which comprises administration of a therapeutically effective amount of a pharmaceutical formulation comprising roflumilast or a pharmaceutical acceptable salt, solvate, or physiologically functional derivative thereof in combination with a pharmaceutical acceptable salt of glycopyrronium, a solvate, or physiologically functional derivative thereof, and a pharmaceutical acceptable carrier and/or one or more excipients.
16. Method according to claim 15, wherein the clinical condition is selected from the group of asthma, nocturnal asthma, exercise-induced asthma, chronic obstructive pulmonary diseases (COPD), chronic and wheezy bronchitis, emphysema, respiratory tract infection and upper respiratory tract disease, rhinitis, allergic and seasonal rhinitis.
17. Method according to claim 16, which comprises a twice daily dosage regimen.
18. Method according to claim 16, which comprises a once daily dosage regimen.
19. Method according to claim 16, which comprises administration of a combination of the a pharmaceutical acceptable salt of glycopyrronium and roflumilast in the same administration form by inhalation from an inhaler and wherein each actuation provides a dose therapeutically effective for a twice daily dosing regimen or for a once daily dosing regimen.

20. Dry powder inhalation product comprising a pharmaceutical composition according to claim 13.

Abstract

This invention relates to pharmaceutical formulations containing combinations of roflumilast and a pharmaceutically acceptable salt of glycopyrronium and the use of such pharmaceutical compositions in medicine, in particular in the prophylaxis and treatment of respiratory disease.